Lunn MPT, Hughes RAC, Wiffen PJ. Duloxetine for treating painful neuropathy or chronic pain. Cochrane Database of Systematic Reviews 2009; Issue 4, Art No CD007115.

Design: Meta-analysis of randomized clinical trials

PICOS:

- Patients: Any kind of painful peripheral neuropathy or chronic pain
- Interventions: All formulations and doses of duloxetine
- Comparisons: Active control medication or placebo, considered separately
- Outcomes: Short term pain relief (12 weeks) compared to baseline using validated pain scales; improvement of 59% or better, improvement of 30% or better, patient's global impression of clinical change (PGIC); adverse effects, long term (more than 12 weeks) pain relief, improvement in any validated Quality of Life Scale by 30% or more
- Study types: Double-blind randomized clinical trials of duloxetine in which duloxetine was administered for at least 8 weeks

Search strategy and study selection:

- Databases included MEDLINE and EMBASE through March 2009, the Cochrane Neuromuscular Disease Group database, the NIH and WHO registry of current clinical trials, and Eli Lilly, the maker of duloxetine
- Two authors independently assessed the studies for risk of bias, using the 2008 Cochrane Handbook method, which estimates risk of bias based upon selection bias (allocation concealment and random sequence generation), performance bias (differences in care other than the intervention of interest), attrition bias (differences in withdrawals from the study), detection bias (differences in how outcomes are determined, requiring blinding of participants and outcome assessors), and reporting bias (selective reporting of outcomes)

Results:

- 14 randomized trials were considered, and 6 trials with 2200 participants were included; 8 were excluded for lack of blinding, for having pain as a secondary outcome, or for being shorter than 8 weeks
- 3 studies were of duloxetine for diabetic neuropathy and 3 were of duloxetine for fibromyalgia
- All 6 studies were sponsored by Eli Lilly
- 5 studies had a dropout rate greater than 20%, which is considered to create at least a moderate risk of bias; only 1 study had a low risk of bias
- For painful neuropathy, 20 mg/d of duloxetine was not more effective than placebo, but 60 mg and 120 mg were both more effective than placebo
- There was not a significant difference between 60 and 120 mg of duloxetine, and the relative benefit of duloxetine for 50% or better pain improvement was 1.65 compared to placebo (improvement was reported for about 47% of

duloxetine patients and for about 29% of placebo patients); the number needed to treat (NNT) is about 6
- For a 30% improvement in pain, both 60 mg/d and 120 mg/d of duloxetine were 1.54 times as beneficial as placebo, with improvement reported in about 66% of duloxetine and in 42% of placebo patients; the NNT is about 5
- The fibromyalgia studies also showed duloxetine 60 or 120 mg better than placebo, with a relative benefit of 1.50 for a 30% improvement in pain, similar to the relative benefit for neuropathic pain; 60 mg and 120 mg doses had similar effects
- Adverse effects were very common in duloxetine at 60 and 120 mg/d doses; at 60 mg, the relative risk of discontinuing the study due to adverse effects was 1.67 compared to placebo; for 120 mg, the relative risk was 2.30
- Commonest adverse effects were nausea, dry mouth, dizziness, somnolence, fatigue, insomnia, constipation, decreased appetite, sweating, and rhinitis

Authors' conclusions:
- There is moderately strong evidence that duloxetine 60 mg and 120 mg are effective in reducing pain from diabetic neuropathy and fibromyalgia, but 20 mg is not likely to be effective
- The effectiveness of duloxetine is similar for diabetic neuropathy and fibromyalgia, but the disorders are dissimilar in pathophysiology and are best considered separately
- The effect of duloxetine in pain reduction is probably independent of its effect as an antidepressant
- Adverse effects are common but mild, requiring few withdrawals

Comments:
- The summary of findings table on pages 3 and 4 clarifies the basis for the estimation of NNT, namely that the assumed response rate for placebo is the median of the rate across studies
- While this is helpful information in understanding the estimation of NNT, the number should be interpreted with caution, since the placebo response rate may differ in different populations with different characteristics; it does not necessarily have a general validity
- Although the authors rate the evidence as "moderately strong" in favor of duloxetine, the summary of findings table clarifies this in the contest of the system that Cochrane is using; "moderate" evidence means that future research is likely to have an important impact on our confidence in the estimate of the effect, and may change the estimate
- As of October 2010, no additional randomized trials of duloxetine for neuropathic pain have been published which could be combined with the included studies for an update of the effect estimate

Assessment: High quality for good evidence that duloxetine is effective and well tolerated for the treatment of neuropathic pain